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(54) Title: NOVEL HUMAN KINASES AND POLYNUCLEOTIDES ENCODING THE SAME

(57) Abstract: Novel human polynucleotide and polypeptide sequences are disclosed that can be used in therapeutic, diagnostic, and pharmacogenomic applications.

NOVEL HUMAN KINASES AND  
POLYNUCLEOTIDES ENCODING THE SAME

The present application claims the benefit of U.S.  
5 Provisional Application Numbers 60/183,582 and 60/184,014 which  
were filed on February 18, 2000 and February 22, 2000,  
respectively, and are herein incorporated by reference in their  
entirety.

1. INTRODUCTION

10 The present invention relates to the discovery,  
identification, and characterization of novel human  
polynucleotides encoding proteins that share sequence similarity  
with mammalian transporter proteins. The invention encompasses  
the described polynucleotides, host cell expression systems, the  
15 encoded proteins, fusion proteins, polypeptides and peptides,  
antibodies to the encoded proteins and peptides, and genetically  
engineered animals that either lack or over express the disclosed  
sequences, antagonists and agonists of the proteins, and other  
compounds that modulate the expression or activity of the proteins  
20 encoded by the disclosed sequences that can be used for diagnosis,  
drug screening, clinical trial monitoring, and treatment of  
diseases and disorders.

2. BACKGROUND OF THE INVENTION

Kinases mediate phosphorylation of a wide variety of proteins  
25 and compounds in the cell. Along with phosphatases, kinases are  
involved in a range of regulatory pathways. Given the  
physiological importance of kinases, they have been subject to  
intense scrutiny and are proven drug targets.

3. SUMMARY OF THE INVENTION

30 The present invention relates to the discovery,  
identification, and characterization of nucleotides that encode  
novel human proteins and the corresponding amino acid sequences of

these proteins. The novel human proteins (NHPs) described for the first time herein share structural similarity with animal kinases, including, but not limited to cell division control protein kinases, serine/threonine protein kinases and membrane-associated  
5 guanylate kinases (MAGUKs). As such, the novel polynucleotides encode a novel kinase family having homologues and orthologs across a range of phyla and species.

The novel human polynucleotides described herein, encode open reading frames (ORFs) encoding proteins of 1,035, 1,214, 1,007,  
10 296, 72, 318, 94, 108, 375, 137, 473, 249, 155, 184, 520, 296, 195, 224, 560, 336, 211, 240, 576, and 352 amino acids in length (see SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48, respectively).

The invention also encompasses agonists and antagonists of  
15 the described NHPs, including small molecules, large molecules, mutant NHPs, or portions thereof, that compete with native NHP, peptides, and antibodies, as well as nucleotide sequences that can be used to inhibit the expression of the described NHPs (e.g., antisense and ribozyme molecules, and gene or regulatory sequence  
20 replacement constructs) or to enhance the expression of the described NHP sequences (e.g., expression constructs that place the described sequence under the control of a strong promoter system), and transgenic animals that express a NHP transgene, or "knock-outs" (which can be conditional) that do not express a  
25 functional NHP. Several knockout ES cell lines have been produced that contain gene trap mutations in murine homologs (or an ortholog of a human homolog) of the described sequences.

Further, the present invention also relates to processes for identifying compounds that modulate, i.e., act as agonists or  
30 antagonists, of NHP expression and/or NHP activity that utilize purified preparations of the described NHPs and/or NHP product, or cells expressing the same. Such compounds can be used as

therapeutic agents for the treatment of any of a wide variety of symptoms associated with biological disorders or imbalances.

#### 4. DESCRIPTION OF THE SEQUENCE LISTING AND FIGURES

5       The Sequence Listing provides the sequences of the described NHP ORFs that encode the described NHP amino acid sequences. Both SEQ ID NO:49 and SEQ ID NO:50 describe full length NHP ORFs as well as flanking 5' and 3' sequences.

#### 10       5. DETAILED DESCRIPTION OF THE INVENTION

      The NHP sequences described in SEQ ID NOS: 1-6 and SEQ ID NOS: 50, were compiled from gene trapped sequences in conjunction with sequences available in GENBANK. These NHPs, described for the first time herein, are novel proteins that are expressed in,  
15   *inter alia*, human cell lines, and human fetal brain, brain, pituitary, cerebellum, thymus, spleen, lymph node, bone marrow, trachea, kidney, liver, fetal liver, prostate, testis, thyroid, adrenal gland, pancreas, salivary gland, stomach, small intestine, colon, uterus, placenta, mammary gland, adipose, esophagus,  
20   bladder, cervix, rectum, pericardium, hypothalamus, ovary, fetal kidney, and fetal lung cells.

      The NHP sequences described in SEQ ID NOS: 7-49 were compiled from gene trapped sequences in conjunction with sequences available in GENBANK, and cDNAs from lung and testis libraries  
25   (Edge Biosystems, Gaithersburg, MD). These NHPs, described for the first time herein, are novel proteins that are expressed in, *inter alia*, human cell lines, and human brain, pituitary, cerebellum, thymus, spleen, lymph node, bone marrow, trachea, kidney, liver, fetal liver, prostate, testis, adrenal gland,  
30   pancreas, salivary gland, stomach, small intestine, colon, skeletal muscle, uterus, placenta, mammary gland, adipose, skin, esophagus, bladder, rectum, thyroid, umbilical vein endothelial cells, and fetal lung cells.

The present invention encompasses the nucleotides presented in the Sequence Listing, host cells expressing such nucleotides, the expression products of such nucleotides, and: (a) nucleotides that encode mammalian homologs of the described sequences, including the specifically described NHPs, and the NHP products; (b) nucleotides that encode one or more portions of the NHPs that correspond to functional domains, and the polypeptide products specified by such nucleotide sequences, including but not limited to the novel regions of any active domain(s); (c) isolated nucleotides that encode mutant versions, engineered or naturally occurring, of the described NHPs in which all or a part of at least one domain is deleted or altered, and the polypeptide products specified by such nucleotide sequences, including but not limited to soluble proteins and peptides in which all or a portion of the signal sequence is deleted; (d) nucleotides that encode chimeric fusion proteins containing all or a portion of a coding region of an NHP, or one of its domains (e.g., a receptor or ligand binding domain, accessory protein/self-association domain, etc.) fused to another peptide or polypeptide; or (e) therapeutic or diagnostic derivatives of the described polynucleotides such as oligonucleotides, antisense polynucleotides, ribozymes, dsRNA, or gene therapy constructs comprising a sequence first disclosed in the Sequence Listing.

As discussed above, the present invention includes: (a) the human DNA sequences presented in the Sequence Listing (and vectors comprising the same) and additionally contemplates any nucleotide sequence encoding a contiguous NHP open reading frame (ORF) that hybridizes to a complement of a DNA sequence presented in the Sequence Listing under highly stringent conditions, e.g., hybridization to filter-bound DNA in 0.5 M NaHPO<sub>4</sub>, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel F.M. et al., eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing

Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3) and encodes a functionally equivalent gene product. Additionally contemplated are any nucleotide sequences that hybridize to the complement of a DNA sequence that encodes and  
5 expresses an amino acid sequence presented in the Sequence Listing under moderately stringent conditions, e.g., washing in 0.2xSSC/0.1% SDS at 42°C (Ausubel et al., 1989, *supra*), yet still encodes a functionally equivalent NHP product. Functional equivalents of a NHP include naturally occurring NHPs present in  
10 other species and mutant NHPs whether naturally occurring or engineered (by site directed mutagenesis, gene shuffling, directed evolution as described in, for example, U.S. Patent No. 5,837,458). The invention also includes degenerate nucleic acid variants of the disclosed NHP polynucleotide sequences.

15 Additionally contemplated are polynucleotides encoding NHP ORFs, or their functional equivalents, encoded by polynucleotide sequences that are about 99, 95, 90, or about 85 percent similar or identical to corresponding regions of the nucleotide sequences of the Sequence Listing (as measured by BLAST sequence comparison  
20 analysis using, for example, the GCG sequence analysis package using standard default settings).

The invention also includes nucleic acid molecules, preferably DNA molecules, that hybridize to, and are therefore the complements of, the described NHP nucleotide sequences. Such  
25 hybridization conditions may be highly stringent or less highly stringent, as described above. In instances where the nucleic acid molecules are deoxyoligonucleotides ("DNA oligos"), such molecules are generally about 16 to about 100 bases long, or about 20 to about 80, or about 34 to about 45 bases long, or any  
30 variation or combination of sizes represented therein that incorporate a contiguous region of sequence first disclosed in the Sequence Listing. Such oligonucleotides can be used in conjunction with the polymerase chain reaction (PCR) to screen

libraries, isolate clones, and prepare cloning and sequencing templates, etc.

Alternatively, such NHP oligonucleotides can be used as hybridization probes for screening libraries, and assessing gene expression patterns (particularly using a micro array or high-throughput "chip" format). Additionally, a series of the described NHP oligonucleotide sequences, or the complements thereof, can be used to represent all or a portion of the described NHP sequences. An oligonucleotide or polynucleotide sequence first disclosed in at least a portion of one or more of the sequences of SEQ ID NOS: 1-50 can be used as a hybridization probe in conjunction with a solid support matrix/substrate (resins, beads, membranes, plastics, polymers, metal or metallized substrates, crystalline or polycrystalline substrates, etc.). Of particular note are spatially addressable arrays (*i.e.*, gene chips, microtiter plates, etc.) of oligonucleotides and polynucleotides, or corresponding oligopeptides and polypeptides, wherein at least one of the biopolymers present on the spatially addressable array comprises an oligonucleotide or polynucleotide sequence first disclosed in at least one of the sequences of SEQ ID NOS: 1-50, or an amino acid sequence encoded thereby. Methods for attaching biopolymers to, or synthesizing biopolymers on, solid support matrices, and conducting binding studies thereon are disclosed in, *inter alia*, U.S. Patent Nos. 5,700,637, 5,556,752, 5,744,305, 4,631,211, 5,445,934, 5,252,743, 4,713,326, 5,424,186, and 4,689,405 the disclosures of which are herein incorporated by reference in their entirety.

Addressable arrays comprising sequences first disclosed in SEQ ID NOS:1-50 can be used to identify and characterize the temporal and tissue specific expression of a gene. These addressable arrays incorporate oligonucleotide sequences of sufficient length to confer the required specificity, yet be within the limitations of the production technology. The length

of these probes is within a range of between about 8 to about 2000 nucleotides. Preferably the probes consist of 60 nucleotides and more preferably 25 nucleotides from the sequences first disclosed in SEQ ID NOS:1-50.

5 For example, a series of the described oligonucleotide sequences, or the complements thereof, can be used in chip format to represent all or a portion of the described sequences. The oligonucleotides, typically between about 16 to about 40 (or any whole number within the stated range) nucleotides in length can  
10 partially overlap each other and/or the sequence may be represented using oligonucleotides that do not overlap. Accordingly, the described polynucleotide sequences shall typically comprise at least about two or three distinct oligonucleotide sequences of at least about 8 nucleotides in  
15 length that are each first disclosed in the described Sequence Listing. Such oligonucleotide sequences can begin at any nucleotide present within a sequence in the Sequence Listing and proceed in either a sense (5'-to-3') orientation vis-a-vis the described sequence or in an antisense orientation.

20 Microarray-based analysis allows the discovery of broad patterns of genetic activity, providing new understanding of gene functions and generating novel and unexpected insight into transcriptional processes and biological mechanisms. The use of addressable arrays comprising sequences first disclosed in SEQ ID  
25 NOS:1-50 provides detailed information about transcriptional changes involved in a specific pathway, potentially leading to the identification of novel components or gene functions that manifest themselves as novel phenotypes.

Probes consisting of sequences first disclosed in SEQ ID  
30 NOS:1-50 can also be used in the identification, selection and validation of novel molecular targets for drug discovery. The use of these unique sequences permits the direct confirmation of drug targets and recognition of drug dependent changes in gene



expression that are modulated through pathways distinct from the drugs intended target. These unique sequences therefore also have utility in defining and monitoring both drug action and toxicity.

As an example of utility, the sequences first disclosed in  
5 SEQ ID NOS:1-50 can be utilized in microarrays or other assay  
formats, to screen collections of genetic material from patients  
who have a particular medical condition. These investigations can  
also be carried out using the sequences first disclosed in SEQ ID  
NOS:1-50 *in silico* and by comparing previously collected genetic  
10 databases and the disclosed sequences using computer software  
known to those in the art.

Thus the sequences first disclosed in SEQ ID NOS:1-50 can be  
used to identify mutations associated with a particular disease  
and also as a diagnostic or prognostic assay.

15 Although the presently described sequences have been  
specifically described using nucleotide sequence, it should be  
appreciated that each of the sequences can uniquely be described  
using any of a wide variety of additional structural attributes,  
or combinations thereof. For example, a given sequence can be  
20 described by the net composition of the nucleotides present within  
a given region of the sequence in conjunction with the presence of  
one or more specific oligonucleotide sequence(s) first disclosed  
in the SEQ ID NOS: 1-50. Alternatively, a restriction map  
specifying the relative positions of restriction endonuclease  
25 digestion sites, or various palindromic or other specific  
oligonucleotide sequences can be used to structurally describe a  
given sequence. Such restriction maps, which are typically  
generated by widely available computer programs (e.g., the  
University of Wisconsin GCG sequence analysis package, SEQUENCHER  
30 3.0, Gene Codes Corp., Ann Arbor, MI, etc.), can optionally be  
used in conjunction with one or more discrete nucleotide  
sequence(s) present in the sequence that can be described by the  
relative position of the sequence relative to one or more

additional sequence(s) or one or more restriction sites present in the disclosed sequence.

For oligonucleotide probes, highly stringent conditions may refer, e.g., to washing in 6xSSC/0.05% sodium pyrophosphate at 5 37°C (for 14-base oligos), 48°C (for 17-base oligos), 55°C (for 20-base oligos), and 60°C (for 23-base oligos). These nucleic acid molecules may encode or act as NHP gene antisense molecules, useful, for example, in NHP gene regulation (for and/or as antisense primers in amplification reactions of NHP gene nucleic 10 acid sequences). With respect to NHP gene regulation, such techniques can be used to regulate biological functions. Further, such sequences may be used as part of ribozyme and/or triple helix sequences that are also useful for NHP gene regulation.

Inhibitory antisense or double stranded oligonucleotides can 15 additionally comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 20 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 25 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 30 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide can also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide will  
5 comprise at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

10 In yet another embodiment, the antisense oligonucleotide is an  $\alpha$ -anomeric oligonucleotide. An  $\alpha$ -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641).  
15 The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330). Alternatively, double stranded RNA can be used to disrupt the expression and function of a targeted NHP.

20 Oligonucleotides of the invention can be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides can be synthesized by the method of Stein et al.  
25 (1988, Nucl. Acids Res. 16:3209), and methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

Low stringency conditions are well known to those of skill in  
30 the art, and will vary predictably depending on the specific organisms from which the library and the labeled sequences are derived. For guidance regarding such conditions see, for example,

Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual (and periodic updates thereof), Cold Springs Harbor Press, N.Y.; and Ausubel et al., 1989, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N.Y.

5       Alternatively, suitably labeled NHP nucleotide probes can be used to screen a human genomic library using appropriately stringent conditions or by PCR. The identification and characterization of human genomic clones is helpful for identifying polymorphisms (including, but not limited to,  
10 nucleotide repeats, microsatellite alleles, single nucleotide polymorphisms, or coding single nucleotide polymorphisms), determining the genomic structure of a given locus/allele, and designing diagnostic tests. For example, sequences derived from regions adjacent to the intron/exon boundaries of the human gene  
15 can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (e.g., splice acceptor and/or donor sites), etc., that can be used in diagnostics and pharmacogenomics.

      Further, a NHP gene homolog can be isolated from nucleic acid  
20 from an organism of interest by performing PCR using two degenerate or "wobble" oligonucleotide primer pools designed on the basis of amino acid sequences within the NHP products disclosed herein. The template for the reaction may be total RNA, mRNA, and/or cDNA obtained by reverse transcription of mRNA  
25 prepared from human or non-human cell lines or tissue known or suspected to express an allele of a NHP gene.

      The PCR product can be subcloned and sequenced to ensure that the amplified sequences represent the sequence of the desired NHP gene. The PCR fragment can then be used to isolate a full length  
30 cDNA clone by a variety of methods. For example, the amplified fragment can be labeled and used to screen a cDNA library, such as a bacteriophage cDNA library. Alternatively, the labeled fragment

can be used to isolate genomic clones via the screening of a genomic library.

PCR technology can also be used to isolate full length cDNA sequences. For example, RNA can be isolated, following standard  
5 procedures, from an appropriate cellular or tissue source (i.e., one known, or suspected, to express a NHP gene). A reverse transcription (RT) reaction can be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis. The  
10 resulting RNA/DNA hybrid may then be "tailed" using a standard terminal transferase reaction, the hybrid may be digested with RNase H, and second strand synthesis may then be primed with a complementary primer. Thus, cDNA sequences upstream of the amplified fragment can be isolated. For a review of cloning  
15 strategies that can be used, see e.g., Sambrook et al., 1989, *supra*.

A cDNA encoding a mutant NHP gene can be isolated, for example, by using PCR. In this case, the first cDNA strand may be synthesized by hybridizing an oligo-dT oligonucleotide to mRNA  
20 isolated from tissue known or suspected to be expressed in an individual putatively carrying a mutant NHP allele, and by extending the new strand with reverse transcriptase. The second strand of the cDNA is then synthesized using an oligonucleotide that hybridizes specifically to the 5' end of the normal gene.  
25 Using these two primers, the product is then amplified via PCR, optionally cloned into a suitable vector, and subjected to DNA sequence analysis through methods well known to those of skill in the art. By comparing the DNA sequence of the mutant NHP allele to that of a corresponding normal NHP allele, the mutation(s)  
30 responsible for the loss or alteration of function of the mutant NHP gene product can be ascertained.

Alternatively, a genomic library can be constructed using DNA obtained from an individual suspected of or known to carry a

mutant NHP allele (e.g., a person manifesting a NHP-associated phenotype such as, for example, obesity, high blood pressure, connective tissue disorders, infertility, etc.), or a cDNA library can be constructed using RNA from a tissue known, or suspected, to  
5 express a mutant NHP allele. A normal NHP gene, or any suitable fragment thereof, can then be labeled and used as a probe to identify the corresponding mutant NHP allele in such libraries. Clones containing mutant NHP gene sequences can then be purified and subjected to sequence analysis according to methods well known  
10 to those skilled in the art.

Additionally, an expression library can be constructed utilizing cDNA synthesized from, for example, RNA isolated from a tissue known, or suspected, to express a mutant NHP allele in an individual suspected of or known to carry such a mutant allele.  
15 In this manner, gene products made by the putatively mutant tissue can be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against a normal NHP product, as described below. (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies: A  
20 Laboratory Manual", Cold Spring Harbor Press, Cold Spring Harbor, NY).

Additionally, screening can be accomplished by screening with labeled NHP fusion proteins, such as, for example, alkaline phosphatase-NHP or NHP-alkaline phosphatase fusion proteins. In  
25 cases where a NHP mutation results in an expressed gene product with altered function (e.g., as a result of a missense or a frameshift mutation), polyclonal antibodies to a NHP are likely to cross-react with a corresponding mutant NHP gene product. Library clones detected via their reaction with such labeled antibodies  
30 can be purified and subjected to sequence analysis according to methods well known in the art.

The invention also encompasses (a) DNA vectors that contain any of the foregoing NHP coding sequences and/or their complements

(i.e., antisense); (b) DNA expression vectors that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences (for example, baculo virus as described in U.S. Patent  
5 No. 5,869,336 herein incorporated by reference); (c) genetically engineered host cells that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences in the host cell; and (d) genetically engineered host cells that express an  
10 endogenous NHP gene under the control of an exogenously introduced regulatory element (i.e., gene activation). As used herein, regulatory elements include, but are not limited to, inducible and non-inducible promoters, enhancers, operators and other elements known to those skilled in the art that drive and regulate  
15 expression. Such regulatory elements include but are not limited to the cytomegalovirus (hCMV) immediate early gene, regulatable, viral elements (particularly retroviral LTR promoters), the early or late promoters of SV40 adenovirus, the *lac* system, the *trp* system, the *TAC* system, the *TRC* system, the major operator and  
20 promoter regions of phage lambda, the control regions of fd coat protein, the promoter for 3-phosphoglycerate kinase (PGK), the promoters of acid phosphatase, and the promoters of the yeast  $\alpha$ -mating factors.

The present invention also encompasses antibodies and anti-  
25 idiotypic antibodies (including Fab fragments), antagonists and agonists of the NHP, as well as compounds or nucleotide constructs that inhibit expression of a NHP gene (transcription factor inhibitors, antisense and ribozyme molecules, or gene or regulatory sequence replacement constructs), or promote the  
30 expression of a NHP (e.g., expression constructs in which NHP coding sequences are operatively associated with expression control elements such as promoters, promoter/enhancers, etc.).

The NHPs or NHP peptides, NHP fusion proteins, NHP nucleotide sequences, antibodies, antagonists and agonists can be useful for the detection of mutant NHPs or inappropriately expressed NHPs for the diagnosis of disease. The NHP proteins or peptides, NHP fusion proteins, NHP nucleotide sequences, host cell expression systems, antibodies, antagonists, agonists and genetically engineered cells and animals can be used for screening for drugs (or high throughput screening of combinatorial libraries) effective in the treatment of the symptomatic or phenotypic manifestations of perturbing the normal function of NHP in the body. The use of engineered host cells and/or animals may offer an advantage in that such systems allow not only for the identification of compounds that bind to the endogenous receptor for an NHP, but can also identify compounds that trigger NHP-mediated activities or pathways.

Finally, the NHP products can be used as therapeutics. For example, soluble derivatives such as NHP peptides/domains corresponding to NHPs, NHP fusion protein products (especially NHP-Ig fusion proteins, *i.e.*, fusions of a NHP, or a domain of a NHP, to an IgFc), NHP antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists or agonists (including compounds that modulate or act on downstream targets in a NHP-mediated pathway) can be used to directly treat diseases or disorders. For instance, the administration of an effective amount of soluble NHP, or a NHP-IgFc fusion protein or an anti-idiotypic antibody (or its Fab) that mimics the NHP could activate or effectively antagonize the endogenous NHP receptor. Nucleotide constructs encoding such NHP products can be used to genetically engineer host cells to express such products *in vivo*; these genetically engineered cells function as "bioreactors" in the body delivering a continuous supply of a NHP, a NHP peptide, or a NHP fusion protein to the body. Nucleotide constructs encoding functional NHPs, mutant NHPs, as well as antisense and ribozyme



molecules can also be used in "gene therapy" approaches for the modulation of NHP expression. Thus, the invention also encompasses pharmaceutical formulations and methods for treating biological disorders.

5        Various aspects of the invention are described in greater detail in the subsections below.

### 5.1 THE NHP SEQUENCES

The cDNA sequences and corresponding deduced amino acid  
10 sequences of the described NHPs are presented in the Sequence Listing. The NHP nucleotide sequences SEQ ID NOS:1-6 were obtained using the sequence information present in human gene trapped sequence tags.

Expression analysis has provided evidence that the described  
15 NHPs can be expressed in human tissues as well as gene trapped human cells. In addition to serine/threonine kinases, the NHPs described in SEQ ID NOS: 1-6 also share significant similarity to a range of additional kinase families such as NEK2 and NY-REN-55 as well as protein kinases from a range of phyla and species.

20        Likewise, the NHPs described in SEQ ID NOS: 7-49 share significant similarity to a range of additional kinase families from a variety of phyla and species, in addition to aforementioned MAGUKs. Two polymorphisms were identified during the sequencing project. The first identified a possible A-G transition at the  
25 sequence position corresponding to, for example, nucleotide 739 of SEQ ID NO: 7 (resulting in a ile-val change at corresponding amino acid position number 247 of, for example, SEQ ID NO:8). Another A-G transition was identified at the sequence position  
corresponding to, for example, nucleotide 67 of SEQ ID NO:9  
30 (resulting in a ile-val change at corresponding amino acid position number 23 of, for example, SEQ ID NO: 10).

Given the physiological importance of protein kinases, they have been subject to intense scrutiny as exemplified and discussed

in U.S. Patent Nos. 5,817,479 and 5,817,479 which describe a variety of uses and applications that can be applied to the described NHP sequences and which are herein incorporated by reference in their entirety.

5

## 5.2 NHPS AND NHP POLYPEPTIDES

NHPs, polypeptides, peptide fragments, mutated, truncated, or deleted forms of the NHPs, and/or NHP fusion proteins can be prepared for a variety of uses. These uses include but are not  
10 limited to the generation of antibodies, as reagents in diagnostic assays, the identification of other cellular gene products related to a NHP, as reagents in assays for screening for compounds that can be used as pharmaceutical reagents useful in the therapeutic treatment of mental, biological, or medical disorders and  
15 diseases. Given the similarity information and expression data, the described NHPs can be targeted (by drugs, oligos, antibodies, etc,) in order to treat disease, or to therapeutically augment the efficacy of, for example, chemotherapeutic agents used in the treatment of breast or prostate cancer.

20 The Sequence Listing discloses the amino acid sequences encoded by the described NHP sequences. The NHPs typically display have initiator methionines in DNA sequence contexts consistent with a translation initiation site.

The NHP amino acid sequences of the invention include the  
25 amino acid sequence presented in the Sequence Listing as well as analogues and derivatives thereof. Further, corresponding NHP homologues from other species are encompassed by the invention. In fact, any NHP protein encoded by the NHP nucleotide sequences described above are within the scope of the invention, as are any  
30 novel polynucleotide sequences encoding all or any novel portion of an amino acid sequence presented in the Sequence Listing. The degenerate nature of the genetic code is well known, and, accordingly, each amino acid presented in the Sequence Listing, is

generically representative of the well known nucleic acid "triplet" codon, or in many cases codons, that can encode the amino acid. As such, as contemplated herein, the amino acid sequences presented in the Sequence Listing, when taken together  
5 with the genetic code (see, for example, Table 4-1 at page 109 of "Molecular Cell Biology", 1986, J. Darnell et al. eds., Scientific American Books, New York, NY, herein incorporated by reference) are generically representative of all the various permutations and combinations of nucleic acid sequences that can encode such amino  
10 acid sequences.

The invention also encompasses proteins that are functionally equivalent to the NHPs encoded by the presently described nucleotide sequences as judged by any of a number of criteria, including, but not limited to, the ability to bind and cleave a  
15 substrate of a NHP, or the ability to effect an identical or complementary downstream pathway, or a change in cellular metabolism (e.g., proteolytic activity, ion flux, tyrosine phosphorylation, etc.). Such functionally equivalent NHP proteins include, but are not limited to, additions or substitutions of  
20 amino acid residues within the amino acid sequence encoded by the NHP nucleotide sequences described above, but which result in a silent change, thus producing a functionally equivalent gene product. Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity,  
25 hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and  
30 glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

A variety of host-expression vector systems can be used to express the NHP nucleotide sequences of the invention. Where, as in the present instance, the NHP peptide or polypeptide is thought to be membrane protein, the hydrophobic regions of the protein can be excised and the resulting soluble peptide or polypeptide can be recovered from the culture media. Such expression systems also encompass engineered host cells that express a NHP, or functional equivalent, *in situ*. Purification or enrichment of a NHP from such expression systems can be accomplished using appropriate detergents and lipid micelles and methods well known to those skilled in the art. However, such engineered host cells themselves may be used in situations where it is important not only to retain the structural and functional characteristics of the NHP, but to assess biological activity, e.g., in drug screening assays.

The expression systems that may be used for purposes of the invention include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing NHP nucleotide sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing NHP nucleotide sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing NHP sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing NHP nucleotide sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian

viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the NHP product being expressed. For example, when a large quantity of such a protein is to be produced for the generation of pharmaceutical compositions of or containing NHP, or for raising antibodies to a NHP, vectors that direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., 1983, EMBO J. 2:1791), in which a NHP coding sequence may be ligated individually into the vector in frame with the *lacZ* coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. 13:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. 264:5503-5509); and the like. pGEX vectors (Pharmacia or American Type Culture Collection) can also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhydrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. A NHP coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter). Successful insertion of NHP coding sequence will result in inactivation of the polyhedrin gene and production of

non-occluded recombinant virus (*i.e.*, virus lacking the proteinaceous coat coded for by the polyhedrin gene). These recombinant viruses are then used to infect *Spodoptera frugiperda* cells in which the inserted gene is expressed (*e.g.*, see Smith et al., 1983, *J. Virol.* 46:584; Smith, U.S. Patent No. 4,215,051).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the NHP nucleotide sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing a NHP product in infected hosts (*e.g.*, See Logan & Shenk, 1984, *Proc. Natl. Acad. Sci. USA* 81:3655-3659). Specific initiation signals may also be required for efficient translation of inserted NHP nucleotide sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where an entire NHP gene or cDNA, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only a portion of a NHP coding sequence is inserted, exogenous translational control signals, including, perhaps, the ATG initiation codon, must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements,

transcription terminators, etc. (See Bitter *et al.*, 1987, *Methods in Enzymol.* 153:516-544).

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies and  
5 processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and  
10 modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript,  
15 glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, human cell lines.

For long-term, high-yield production of recombinant proteins,  
20 stable expression is preferred. For example, cell lines which stably express the NHP sequences described above can be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g.,  
25 promoter, enhancer sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the  
30 recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer

cell lines which express the NHP product. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the NHP product.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler, et al., 1977, *Cell* 11:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1962, *Proc. Natl. Acad. Sci. USA* 48:2026), and adenine phosphoribosyltransferase (Lowy, et al., 1980, *Cell* 22:817) genes can be employed in tk<sup>-</sup>, hgp<sup>r</sup>t<sup>-</sup> or apr<sup>t</sup>- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler, et al., 1980, *Natl. Acad. Sci. USA* 77:3567; O'Hare, et al., 1981, *Proc. Natl. Acad. Sci. USA* 78:1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, *Proc. Natl. Acad. Sci. USA* 78:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin, et al., 1981, *J. Mol. Biol.* 150:1); and hyg<sup>r</sup>, which confers resistance to hygromycin (Santerre, et al., 1984, *Gene* 30:147).

Alternatively, any fusion protein can be readily purified by utilizing an antibody specific for the fusion protein being expressed. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht, et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972-8976). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the gene's open reading frame is translationally fused to an amino-terminal tag consisting of six histidine residues. Extracts from cells infected with recombinant vaccinia virus are loaded onto Ni<sup>2+</sup> nitriloacetic acid-agarose columns and histidine-tagged proteins are selectively eluted with imidazole-containing buffers.



Also encompassed by the present invention are fusion proteins that direct the NHP to a target organ and/or facilitate transport across the membrane into the cytosol. Conjugation of NHPs to antibody molecules or their Fab fragments could be used to target  
5 cells bearing a particular epitope. Attaching the appropriate signal sequence to the NHP would also transport the NHP to the desired location within the cell. Alternatively targeting of NHP or its nucleic acid sequence might be achieved using liposome or lipid complex based delivery systems. Such technologies are  
10 described in Liposomes: A Practical Approach, New, RRC ed., Oxford University Press, New York and in U.S. Patents Nos. 4,594,595, 5,459,127, 5,948,767 and 6,110,490 and their respective disclosures which are herein incorporated by reference in their entirety. Additionally embodied are novel protein constructs  
15 engineered in such a way that they facilitate transport of the NHP to the target site or desired organ, where they cross the cell membrane and/or the nucleus where the NHP can exert its functional activity. This goal may be achieved by coupling of the NHP to a cytokine or other ligand that provides targeting specificity,  
20 and/or to a protein transducing domain (see generally U.S. applications Ser. No. 60/111,701 and 60/056,713, both of which are herein incorporated by reference, for examples of such transducing sequences) to facilitate passage across cellular membranes and can optionally be engineered to include nuclear localization  
25 sequences.

### 5.3 ANTIBODIES TO NHP PRODUCTS

Antibodies that specifically recognize one or more epitopes of a NHP, or epitopes of conserved variants of a NHP, or peptide  
30 fragments of a NHP are also encompassed by the invention. Such antibodies include but are not limited to polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')<sub>2</sub> fragments,

fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

The antibodies of the invention may be used, for example, in the detection of NHP in a biological sample and may, therefore, be utilized as part of a diagnostic or prognostic technique whereby patients may be tested for abnormal amounts of NHP. Such antibodies may also be utilized in conjunction with, for example, compound screening schemes for the evaluation of the effect of test compounds on expression and/or activity of a NHP gene product. Additionally, such antibodies can be used in conjunction gene therapy to, for example, evaluate the normal and/or engineered NHP-expressing cells prior to their introduction into the patient. Such antibodies may additionally be used as a method for the inhibition of abnormal NHP activity. Thus, such antibodies may, therefore, be utilized as part of treatment methods.

For the production of antibodies, various host animals may be immunized by injection with a NHP, an NHP peptide (e.g., one corresponding to a functional domain of an NHP), truncated NHP polypeptides (NHP in which one or more domains have been deleted), functional equivalents of the NHP or mutated variant of the NHP. Such host animals may include but are not limited to pigs, rabbits, mice, goats, and rats, to name but a few. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not limited to Freund's adjuvant (complete and incomplete), mineral salts such as aluminum hydroxide or aluminum phosphate, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. Alternatively, the immune response could be enhanced by combination and or coupling with molecules such as keyhole limpet

hemocyanin, tetanus toxoid, diphtheria toxoid, ovalbumin, cholera toxin or fragments thereof. Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of the immunized animals.

5        Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, can be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, (1975, 10 Nature 256:495-497; and U.S. Patent No. 4,376,110), the human B-cell hybridoma technique (Kosbor et al., 1983, Immunology Today 4:72; Cole et al., 1983, Proc. Natl. Acad. Sci. USA 80:2026-2030), and the EBV-hybridoma technique (Cole et al., 1985, Monoclonal Antibodies And Cancer Therapy, Alan R. Liss, Inc., pp. 77-96).  
15 Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated *in vitro* or *in vivo*. Production of high titers of mAbs *in vivo* makes this the presently preferred method of production.

20        In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., 1984, Proc. Natl. Acad. Sci., 81:6851-6855; Neuberger et al., 1984, Nature, 312:604-608; Takeda et al., 1985, Nature, 314:452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity  
25 together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region.  
30 Such technologies are described in U.S. Patents Nos. 6,075,181 and 5,877,397 and their respective disclosures which are herein incorporated by reference in their entirety. Also encompassed by

the present invention is the use of fully humanized monoclonal antibodies as described in US Patent No. 6,150,584 and respective disclosures which are herein incorporated by reference in their entirety.

5       Alternatively, techniques described for the production of single chain antibodies (U.S. Patent 4,946,778; Bird, 1988, Science 242:423-426; Huston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; and Ward et al., 1989, Nature 341:544-546) can be adapted to produce single chain antibodies against NHP gene  
10 products. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, such fragments  
15 include, but are not limited to: the F(ab')<sub>2</sub> fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the F(ab')<sub>2</sub> fragments. Alternatively, Fab expression libraries may be constructed (Huse et al., 1989, Science,  
20 246:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Antibodies to a NHP can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" a given NHP, using techniques well known to those skilled in the art. (See, e.g.,  
25 Greenspan & Bona, 1993, FASEB J 7(5):437-444; and Nissinoff, 1991, J. Immunol. 147(8):2429-2438). For example antibodies which bind to a NHP domain and competitively inhibit the binding of NHP to its cognate receptor can be used to generate anti-idiotypes that "mimic" the NHP and, therefore, bind and activate or neutralize a  
30 receptor. Such anti-idiotypic antibodies or Fab fragments of such anti-idiotypes can be used in therapeutic regimens involving a NHP mediated pathway.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the  
5 scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims. All cited publications, patents,  
10 and patent applications are herein incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed  
5 in SEQ ID NO: 1.
2. An isolated nucleic acid molecule comprising a nucleotide sequence that:
  - (a) encodes the amino acid sequence shown in SEQ ID  
10 NO: 2; and
  - (b) hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.
- 15 3. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:2.
- 20 4. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:4.
- 25 5. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:6.
- 30 6. An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in SEQ ID NO: 45.
7. An isolated nucleic acid molecule comprising a nucleotide sequence that:

- (a) encodes the amino acid sequence shown in SEQ ID NO: 46; and
- (b) hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO: 45 or the complement thereof.

5

8. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:46.

10

9. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:38.

15

10. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:30

## SEQUENCE LISTING

&lt;110&gt; LEXICON GENETICS INCORPORATED

&lt;120&gt; Novel Human Kinases and Polynucleotides Encoding the Same

&lt;130&gt; LEX-0137-PCT

&lt;150&gt; US 60/183,582

&lt;151&gt; 2000-02-18

&lt;150&gt; US 60/184,014

&lt;151&gt; 2000-02-22

&lt;160&gt; 50

&lt;170&gt; FastSEQ for Windows Version 4.0

&lt;210&gt; 1

&lt;211&gt; 3108

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 1

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&lt;210&gt; 2

&lt;211&gt; 1035

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 2

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Ser Leu His Tyr Ser Tyr Asp Leu Arg Ser Leu Val Ser Gln Leu Phe
 20             25             30
Lys Arg Asn Pro Arg Asp Arg Pro Ser Val Asn Ser Ile Leu Glu Lys
 35             40             45
Gly Phe Ile Ala Lys Arg Ile Glu Lys Phe Leu Ser Pro Gln Leu Ile
 50             55             60
Ala Glu Glu Phe Cys Leu Lys Thr Phe Ser Lys Phe Gly Ser Gln Pro
 65             70             75             80
Ile Pro Ala Lys Arg Pro Ala Ser Gly Gln Asn Ser Ile Ser Val Met
 85             90             95
Pro Ala Gln Lys Ile Thr Lys Pro Ala Ala Lys Tyr Gly Ile Pro Leu
100            105            110
Ala Tyr Lys Lys Tyr Gly Asp Lys Lys Leu His Glu Lys Lys Pro Leu
115            120            125
Gln Lys His Lys Gln Ala His Gln Thr Pro Glu Lys Arg Val Asn Thr
130            135            140
Gly Glu Glu Arg Arg Lys Ile Ser Glu Glu Ala Arg Lys Arg Arg
145            150            155            160
Leu Glu Phe Ile Glu Lys Glu Lys Lys Gln Lys Asp Gln Ile Ile Ser
165            170            175
Leu Met Lys Ala Glu Gln Met Lys Arg Gln Glu Lys Glu Arg Leu Glu
180            185            190
Arg Ile Asn Arg Ala Arg Glu Gln Gly Trp Arg Asn Val Leu Ser Ala
195            200            205
Gly Gly Ser Gly Glu Val Lys Ala Pro Phe Leu Gly Ser Gly Gly Thr
210            215            220

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Lys Trp Lys Arg Glu Ile Tyr Gly Arg Gly Leu Pro Glu Arg Gln Lys
                260                265                270
Gly Gln Leu Ala Val Glu Arg Ala Lys Gln Val Glu Glu Phe Leu Gln
                275                280                285
Arg Lys Arg Glu Ala Met Gln Asn Lys Ala Arg Ala Glu Gly His Met
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gaaactcagt	cggcagatag	gataccattt	caggaaaatg	aagtttctga	agatggagtc	2100
tcgagtactg	tggaccaact	tagtgacatt	catatagagc	ctggaaccaa	tgattctcag	2160
cactctaaat	gtgatgtaga	taagtctgtg	caaccggaac	catttttcca	taagggtggt	2220
cattctgaac	acttgaactt	agtccctcaa	gttcaatcag	ttcagtgttc	accagaagaa	2280
tcttttgcac	ttcgatctca	ctcgcattta	ccaccaaaaa	ataaaaacaa	gaattccttg	2340
ctgattggac	tttcaactgg	tctgtttgat	gcaacaacc	caaagatgtt	aaggacatgt	2400
tcacttccag	atctctcaaa	gctgttcaga	acccttatgg	atgttcccac	cgtaggagat	2460
gttcgtcaag	acaatcttga	aatagatgaa	attaagatg	aaaacattaa	agaaggacct	2520
tctgattctg	aagacattgt	gtttgaagaa	actgacacag	atttacaaga	gctgcaggcc	2580
tcgatggaac	agttacttag	ggaacaacct	ggtgaagaat	acagtgaaga	agaagagtca	2640
gtcttgaaga	acagtgatgt	ggagccaact	gcaaatggga	cagatgtggc	agatgaagat	2700
gacaatocca	gtagtgaag	tgccctgaac	gaagaatggc	actcagataa	cagtgatggt	2760
gaaattgcta	gtgaatgtga	atgcgatagt	gtctttaacc	atttagagga	actgagactt	2820
catctggagc	aggaaatggg	ctttgaaaaa	ttctttgagg	tttatgagaa	aataaaggct	2880
attcatgaag	atgaagatga	aaatattgaa	atttgttcaa	aaatagttca	aaatattttg	2940
ggaaatgaac	atcagcatct	ttatgccaa	attcttcatt	tagtcatggc	agatggagcc	3000
taccaagaag	ataatgatga	ataa				3024

&lt;210&gt; 6

&lt;211&gt; 1007

&lt;212&gt; PRT

&lt;213&gt; homo sapiens



&lt;400&gt; 6

```

Met Lys Asn Leu Val Leu Lys Ile Ile Ser Gly Ser Phe Pro Pro Val
 1           5           10           15
Ser Leu His Tyr Ser Tyr Asp Leu Arg Ser Leu Val Ser Gln Leu Phe
      20           25           30
Lys Arg Asn Pro Arg Asp Arg Pro Ser Val Asn Ser Ile Leu Glu Lys
      35           40           45
Gly Phe Ile Ala Lys Arg Ile Glu Lys Phe Leu Ser Pro Gln Leu Ile
      50           55           60
Ala Glu Glu Phe Cys Leu Lys Thr Phe Ser Lys Phe Gly Ser Gln Pro
65           70           75           80
Ile Pro Ala Lys Arg Pro Ala Ser Gly Gln Asn Ser Ile Ser Val Met
      85           90           95
Pro Ala Gln Lys Ile Thr Lys Pro Ala Ala Lys Tyr Gly Ile Pro Leu
      100          105          110
Ala Tyr Lys Lys Tyr Gly Asp Lys Lys Leu His Glu Lys Lys Pro Leu
      115          120          125
Gln Lys His Lys Gln Ala His Gln Thr Pro Glu Lys Arg Val Asn Thr
      130          135          140
Gly Glu Glu Arg Arg Lys Ile Ser Glu Glu Ala Ala Arg Lys Arg Arg
145          150          155          160
Leu Glu Phe Ile Glu Lys Glu Lys Lys Gln Lys Asp Gln Ile Ile Ser
      165          170          175
Leu Met Lys Ala Glu Gln Met Lys Arg Gln Glu Lys Glu Arg Leu Glu
      180          185          190
Arg Ile Asn Arg Ala Arg Glu Gln Gly Trp Arg Asn Val Leu Ser Ala
      195          200          205
Gly Gly Ser Gly Glu Val Lys Ala Pro Phe Leu Gly Ser Gly Gly Thr
      210          215          220
Ile Ala Pro Ser Ser Phe Ser Ser Arg Gly Gln Tyr Glu His Tyr His
225          230          235          240
Ala Ile Phe Asp Gln Met Gln Gln Gln Arg Ala Glu Asp Asn Glu Ala
      245          250          255
Lys Trp Lys Arg Glu Ile Tyr Gly Arg Gly Leu Pro Glu Arg Gln Lys
      260          265          270
Gly Gln Leu Ala Val Glu Arg Ala Lys Gln Val Glu Glu Phe Leu Gln
      275          280          285
Arg Lys Arg Glu Ala Met Gln Asn Lys Ala Arg Ala Glu Gly His Met
      290          295          300
Val Tyr Leu Ala Arg Leu Arg Gln Ile Arg Leu Gln Asn Phe Asn Glu
305          310          315          320
Arg Gln Gln Ile Lys Ala Lys Leu Arg Gly Glu Lys Lys Glu Ala Asn
      325          330          335
His Ser Glu Gly Gln Glu Gly Ser Glu Glu Ala Asp Met Arg Arg Lys
      340          345          350
Lys Ile Glu Ser Leu Lys Ala His Ala Asn Ala Arg Ala Ala Val Leu
      355          360          365
Lys Glu Gln Leu Glu Arg Lys Arg Lys Glu Ala Tyr Glu Arg Glu Lys
      370          375          380
Lys Val Trp Glu Glu His Leu Val Ala Lys Gly Val Lys Ser Ser Asp
385          390          395          400
Val Ser Pro Pro Leu Gly Gln His Glu Thr Gly Gly Ser Pro Ser Lys
      405          410          415
Gln Gln Met Arg Ser Val Ile Ser Val Thr Ser Ala Leu Lys Glu Val
      420          425          430
Gly Val Asp Ser Ser Leu Thr Asp Thr Arg Glu Thr Ser Glu Glu Met

```

435		440		445	
Gln Lys Thr Asn Asn Ala Ile Ser Ser Lys Arg Glu Ile Leu Arg Arg					
450		455		460	
Leu Asn Glu Asn Leu Lys Ala Gln Glu Asp Glu Lys Gly Met Gln Asn					
465		470		475	480
Leu Ser Asp Thr Phe Glu Ile Asn Val His Glu Asp Ala Lys Glu His					
	485		490		495
Glu Lys Glu Lys Ser Val Ser Ser Asp Arg Lys Lys Trp Glu Ala Gly					
	500		505		510
Gly Gln Leu Val Ile Pro Leu Asp Glu Leu Thr Leu Asp Thr Ser Phe					
	515		520		525
Ser Thr Thr Glu Arg His Thr Val Gly Glu Val Ile Lys Leu Gly Pro					
	530		535		540
Asn Gly Ser Pro Arg Arg Ala Trp Gly Lys Ser Pro Thr Asp Ser Val					
545		550		555	560
Leu Lys Ile Leu Gly Glu Ala Glu Leu Gln Leu Gln Thr Glu Leu Leu					
	565		570		575
Glu Asn Thr Thr Ile Arg Ser Glu Ile Ser Pro Glu Gly Glu Lys Tyr					
	580		585		590
Lys Pro Leu Ile Thr Gly Glu Lys Lys Val Gln Cys Ile Ser His Glu					
	595		600		605
Ile Asn Pro Ser Ala Ile Val Asp Ser Pro Val Glu Thr Lys Ser Pro					
	610		615		620
Glu Phe Ser Glu Ala Ser Pro Gln Met Ser Leu Lys Leu Glu Gly Asn					
625		630		635	640
Leu Glu Glu Pro Asp Asp Leu Glu Thr Glu Ile Leu Gln Glu Pro Ser					
	645		650		655
Gly Thr Asn Lys Asp Glu Ser Leu Pro Cys Thr Ile Thr Asp Val Trp					
	660		665		670
Ile Ser Glu Glu Lys Glu Thr Lys Glu Thr Gln Ser Ala Asp Arg Ile					
	675		680		685
Thr Ile Gln Glu Asn Glu Val Ser Glu Asp Gly Val Ser Ser Thr Val					
	690		695		700
Asp Gln Leu Ser Asp Ile His Ile Glu Pro Gly Thr Asn Asp Ser Gln					
705		710		715	720
His Ser Lys Cys Asp Val Asp Lys Ser Val Gln Pro Glu Pro Phe Phe					
	725		730		735
His Lys Val Val His Ser Glu His Leu Asn Leu Val Pro Gln Val Gln					
	740		745		750
Ser Val Gln Cys Ser Pro Glu Glu Ser Phe Ala Phe Arg Ser His Ser					
	755		760		765
His Leu Pro Pro Lys Asn Lys Asn Lys Asn Ser Leu Leu Ile Gly Leu					
	770		775		780
Ser Thr Gly Leu Phe Asp Ala Asn Asn Pro Lys Met Leu Arg Thr Cys					
785		790		795	800
Ser Leu Pro Asp Leu Ser Lys Leu Phe Arg Thr Leu Met Asp Val Pro					
	805		810		815
Thr Val Gly Asp Val Arg Gln Asp Asn Leu Glu Ile Asp Glu Ile Lys					
	820		825		830
Asp Glu Asn Ile Lys Glu Gly Pro Ser Asp Ser Glu Asp Ile Val Phe					
	835		840		845
Glu Glu Thr Asp Thr Asp Leu Gln Glu Leu Gln Ala Ser Met Glu Gln					
	850		855		860
Leu Leu Arg Glu Gln Pro Gly Glu Glu Tyr Ser Glu Glu Glu Glu Ser					
865		870		875	880
Val Leu Lys Asn Ser Asp Val Glu Pro Thr Ala Asn Gly Thr Asp Val					

```

      885              890              895
Ala Asp Glu Asp Asp Asn Pro Ser Ser Glu Ser Ala Leu Asn Glu Glu
      900              905              910
Trp His Ser Asp Asn Ser Asp Gly Glu Ile Ala Ser Glu Cys Glu Cys
      915              920              925
Asp Ser Val Phe Asn His Leu Glu Glu Leu Arg Leu His Leu Glu Gln
      930              935              940
Glu Met Gly Phe Glu Lys Phe Phe Glu Val Tyr Glu Lys Ile Lys Ala
      945              950              955              960
Ile His Glu Asp Glu Asp Glu Asn Ile Glu Ile Cys Ser Lys Ile Val
      965              970              975
Gln Asn Ile Leu Gly Asn Glu His Gln His Leu Tyr Ala Lys Ile Leu
      980              985              990
His Leu Val Met Ala Asp Gly Ala Tyr Gln Glu Asp Asn Asp Glu
      995              1000              1005

```

<210> 7  
 <211> 891  
 <212> DNA  
 <213> homo sapiens

```

<400> 7
atgccagctt tgtcaacggg atctgggagt gacactgggc tgtatgagct gttggctgct      60
ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat      120
atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat      180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttgcccga tgatctggcc      240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca      300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac      360
ccagtgttgc ctctatgccc tgaagatatt gacgatgagg aagactcagt aaaaataatc      420
cgtctggcca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg      480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat      540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaag gcctgaggaa      600
ataatacaga ttttggtcca gtctcaggga gcaattacat ttaagattat acccggcagc      660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat      720
cctaagtagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaaggagat      780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat      840
gccaaccca gggcaggctt gatccctca aagcatttcc aggaaagggtg a      891

```

<210> 8  
 <211> 296  
 <212> PRT  
 <213> homo sapiens

```

<400> 8
Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu
  1              5              10              15
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln
      20              25              30
Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His
      35              40              45
Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser
      50              55              60
Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala
      65              70              75              80
Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu

```

```

      85              90              95
Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp
      100              105              110
Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu
      115              120              125
Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys
      130              135              140
Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly
      145              150              155              160
Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser
      165              170              175
Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro
      180              185              190
Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser
      195              200              205
Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr
      210              215              220
Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
      225              230              235              240
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
      245              250              255
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
      260              265              270
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
      275              280              285
Pro Ser Lys His Phe Gln Glu Arg
      290              295

```

&lt;210&gt; 9

&lt;211&gt; 219

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 9

```

atgaaacttt tcttcagat gtttatcaaa gccctctttg actataatcc taatgaggat      60
aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt      120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caaccccagg      180
gcaggcttga tccctcaaaa gcatttccag gaaaggtga                               219

```

&lt;210&gt; 10

&lt;211&gt; 72

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 10

```

Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
  1              5              10              15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
      20              25              30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
      35              40              45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
      50              55              60
Pro Ser Lys His Phe Gln Glu Arg
      65              70

```

<210> 11  
 <211> 957  
 <212> DNA  
 <213> homo sapiens

<400> 11  
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 ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat 120  
 atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat 180  
 gagaagcaga gtccgggtgcc cattctccat ggtgcggcgg ccttggccga tgatctggcc 240  
 gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca 300  
 aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac 360  
 ccagtgttgc ctctatgccc tgaagatatt gacgatgagg aagactcagt aaaaataatc 420  
 cgtctgggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg 480  
 gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat 540  
 gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaaag gcctgaggaa 600  
 ataatacaga ttttggtcga gtctcagggg gcaattacat ttaagattat acccggcagc 660  
 aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat 720  
 cctaagtagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaagggagat 780  
 attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat 840  
 gccaacccca gggcaggctt gatccctca aagcatttcc aggaaaggag attggtttg 900  
 agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atcctaa 957

<210> 12  
 <211> 318  
 <212> PRT  
 <213> homo sapiens

<400> 12  
 Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu  
 1 5 10 15  
 Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln  
 20 25 30  
 Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His  
 35 40 45  
 Ser Leu Val Lys Ile His Gly Lys Leu His Tyr Tyr Glu Lys Gln Ser  
 50 55 60  
 Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala  
 65 70 75 80  
 Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu  
 85 90 95  
 Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp  
 100 105 110  
 Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu  
 115 120 125  
 Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys  
 130 135 140  
 Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly  
 145 150 155 160  
 Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser  
 165 170 175  
 Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro  
 180 185 190  
 Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser  
 195 200 205  
 Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr

```

      210              215              220
Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
225              230              235              240
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
      245              250              255
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
      260              265              270
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
      275              280              285
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
      290              295              300
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser
305              310              315

```

<210> 13  
 <211> 285  
 <212> DNA  
 <213> homo sapiens

```

<400> 13
atgaaacttt tcttcagat gtttatcaaa gccctctttg actataatcc taatgaggat      60
aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt      120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caaccccagg      180
gcaggttga tccccataaa gcatttccag gaaaggagat tggctttgag acgaccagaa      240
atattggttc agcccctgaa agtttccaac aggaaatcat cctaa                      285

```

<210> 14  
 <211> 94  
 <212> PRT  
 <213> homo sapiens

```

<400> 14
Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
  1              5              10              15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
      20              25              30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
      35              40              45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
      50              55              60
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
      65              70              75              80
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser
      85              90

```

<210> 15  
 <211> 327  
 <212> DNA  
 <213> homo sapiens

```

<400> 15
atgtgctgcc caaagactgc ttgcagaggt cccgtgggag tagggctgaa tgaactgaaa      60
cgaaagctgc tgatcagtga caccagcac tatggcgtga cagtgcccca taccaccaga      120
gcaagaagaa gccaggagag tgatggtgtt gaatacattt tcatttccaa gcatttgttt      180
gagacagatg tacaaaataa caagtttatt gaatatggag aatataaaaa caactactac      240
ggcacaagta tagactcagt tcggtctgtc ctgtctaaaa acaaagtttg tttgttgat      300

```

gttcagcctc atgtaagtaa acaatga

327

&lt;210&gt; 16

&lt;211&gt; 108

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 16

```

Met Cys Cys Pro Lys Thr Ala Cys Arg Gly Pro Val Gly Val Gly Leu
 1           5           10           15
Asn Glu Leu Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly
      20           25           30
Val Thr Val Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp
      35           40           45
Gly Val Glu Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val
 50           55           60
Gln Asn Asn Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr
65           70           75           80
Gly Thr Ser Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val
      85           90           95
Cys Leu Leu Asp Val Gln Pro His Val Ser Lys Gln
      100           105

```

&lt;210&gt; 17

&lt;211&gt; 1128

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 17

```

atgccagctt tgtcaacggg atctgggagt gacactggtc tgtatgagct gttggctgct      60
ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat      120
atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat      180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttggccga tgatctggcc      240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca      300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac      360
ccagtgttgc ctccatagcc tgaagatatt gacgatgagg aagactcagt aaaaataatc      420
cgtctggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg      480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat      540
gttggtgatg aacctaggga agtcaacggg ataccagtgg aggataaaaag gcctgaggaa      600
ataatacaga ttttggtctc gtctcaggga gcaattacat ttaagattat acccggcagc      660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat      720
cctaattgagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaaggagat      780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat      840
gccaaaccca gggcaggctt gatccctcca aagcatttcc aggaaaggag attggctttg      900
agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atctggtttt      960
agaagaagtt ttcgtcttag tagaaaagat aagaaaacaa ataaatccat gtatgaatgc     1020
aagaagagtg atcagtacga cacagctgac gtaccacat acgaagaagt gacaccgtat     1080
cggcgacaaa ctaatgaaaa atacagactc gttgtcttgg ttgcttga      1128

```

&lt;210&gt; 18

&lt;211&gt; 375

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 18

```

Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu

```

```

      1              5              10              15
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln
      20              25              30
Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His
      35              40              45
Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser
      50              55              60
Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala
      65              70              75              80
Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu
      85              90              95
Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp
      100              105              110
Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu
      115              120              125
Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys
      130              135              140
Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly
      145              150              155              160
Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser
      165              170              175
Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro
      180              185              190
Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser
      195              200              205
Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr
      210              215              220
Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
      225              230              235              240
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
      245              250              255
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
      260              265              270
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
      275              280              285
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
      290              295              300
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
      305              310              315              320
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
      325              330              335
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
      340              345              350
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
      355              360              365
Arg Leu Val Val Leu Val Ala
      370              375

```

&lt;210&gt; 19

&lt;211&gt; 414

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 19

```

atgtatgaat gcaagaagag tgatcagtac gacacagctg acgtaccac atacgaagaa
gtgacaccgt atcggcgaca aactaatgaa aaatacagac tcgttgtctt gggtgtgcc

```

60

120



gtgggagtag ggctgaatga actgaaacga aagctgctga tcagtgcacac ccagcactat	180
ggcgtgacag tgccccatac caccagagca agaagaagcc aggagagtga tgggtgtgaa	240
tacattttca tttccaagca tttgtttgag acagatgtac aaaataacaa gtttattgaa	300
tatggagaat ataaaaacaa ctactacggc acaagtatag actcagttcg gtctgtcctt	360
gctaaaaaca aagttttgtt gttggatgtt cagcctcatg taagtaaaca atga	414

&lt;210&gt; 20

&lt;211&gt; 137

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 20

Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro	
1 5 10 15	
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr	
20 25 30	
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu	
35 40 45	
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val	
50 55 60	
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu	
65 70 75 80	
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn	
85 90 95	
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser	
100 105 110	
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu	
115 120 125	
Asp Val Gln Pro His Val Ser Lys Gln	
130 135	

&lt;210&gt; 21

&lt;211&gt; 1422

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 21

atgccagctt tgtcaacggg atctgggagt gacactggtc tgtatgagct gttggctgct	60
ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat	120
atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat	180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttggccga tgatctggcc	240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca	300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac	360
ccagtgttgc ctccatgcc tgaagatatt gacgatgagg aagactcagt aaaaataatc	420
cgtctggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg	480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat	540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaag gcctgaggaa	600
ataatacaga ttttggctca gtctcaggga gcaattacat ttaagattat acccggcagc	660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat	720
cctaattgagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaaggagat	780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat	840
gccaacccca gggcaggctt gatccctca aagcatttcc aggaaaggag attggctttg	900
agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atctggtttt	960
agaagaagtt ttcgtcttag tagaaaagat aagaaaacaa ataaatccat gtatgaatgc	1020
aagaagagtg atcagtacga cacagctgac gtaccacat acgaagaagt gacaccgtat	1080
cggcgacaaa ctaatgaaaa atacagactc gttgtcttgg ttggtcccggt gggagtaggg	1140

```

Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
      355                360                365
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
  370                375                380
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
385                390                395                400
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
      405                410                415
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
      420                425                430
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
      435                440                445
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
      450                455                460
Asp Val Gln Pro His Val Ser Lys Gln
465                470

```

&lt;210&gt; 23

&lt;211&gt; 750

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 23

```

atgaaacttt tcttcagat gtttatcaaa gccctctttg actataatcc taatgaggat      60
aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt      120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caacccagg      180
gcaggcttga tccctcaaa gcatttcag gaaaggagat tggctttgag acgaccagaa      240
atattggttc agcccctgaa agtttccaac aggaaatcat ctggttttag aagaagtttt      300
cgtcttagta gaaaagataa gaaaacaaat aaatccatgt atgaatgcaa gaagagtgtat      360
cagtacgaca cagctgacgt acccacatac gaagaagtga caccgtatcg gcgacaaact      420
aatgaaaaat acagactcgt tgtcttggtt ggtcccgtgg gagtagggct gaatgaactg      480
aaacgaaagc tgctgatcag tgacaccag cactatggcg tgacagtgcc ccataccacc      540
agagcaagaa gaagccagga gagtgatggt gttgaatata ttttcatttc caagcatttg      600
tttgagacag atgtacaaaa taacaagttt attgaatatg gagaataata aaacaactac      660
tacggcacaa gtatagactc agttcgtct gtccttgcta aaaacaaagt ttgtttgttg      720
gatgttcagc ctcatgtaag taaacaatga                                750

```

&lt;210&gt; 24

&lt;211&gt; 249

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 24

```

Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
  1                5                10                15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
      20                25                30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
      35                40                45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
      50                55                60
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
      65                70                75                80
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
      85                90                95
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser

```

```

      100      105      110
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
      115      120      125
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
      130      135      140
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
145      150      155      160
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
      165      170      175
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
      180      185      190
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
      195      200      205
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
      210      215      220
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
225      230      235      240
Asp Val Gln Pro His Val Ser Lys Gln
      245

```

<210> 25  
 <211> 468  
 <212> DNA  
 <213> homo sapiens

```

<400> 25
atgtgctgcc caaagactgc ttgcagaggt cccgtgggag tagggctgaa tgaactgaaa      60
cgaaagctgc tgatcagtga caccagcac tatggcgtga cagtgcccca taccaccaga      120
gcaagaagaa gccaggagag tgatggtgtt gaatacattt tcatttccaa gcatttgttt      180
gagacagatg tacaaaaataa caagtttatt gaatatggag aatataaaaa caactactac      240
ggcacaaagta tagactcagt tcggtctgtc cttgctaaaa acaaagtttg tttgttgat      300
gttcagcctc atacagtga gcatTTaagg acactagaat ttaagcccta tgtgatattt      360
ataaagcctc catcaataga gcgtttgaga gaaacaagaa aaaatgcaaa gattatttca      420
agcagagatg accaaggtgc tgcaaaaccc ttcacacaag gagaatag      468

```

<210> 26  
 <211> 155  
 <212> PRT  
 <213> homo sapiens

```

<400> 26
Met Cys Cys Pro Lys Thr Ala Cys Arg Gly Pro Val Gly Val Gly Leu
 1      5      10      15
Asn Glu Leu Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly
      20      25      30
Val Thr Val Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp
      35      40      45
Gly Val Glu Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val
      50      55      60
Gln Asn Asn Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr
65      70      75      80
Gly Thr Ser Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val
      85      90      95
Cys Leu Leu Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu
      100      105      110
Glu Phe Lys Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg

```

115                      120                      125  
 Leu Arg Glu Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp  
 130                      135                      140  
 Gln Gly Ala Ala Lys Pro Phe Thr Gln Gly Glu  
 145                      150                      155

&lt;210&gt; 27

&lt;211&gt; 555

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 27

atgtatgaat	gcaagaagag	tgatcagtag	gacacagctg	acgtacccac	atacgaagaa	60
gtgacaccgt	atcggcgaca	aactaatgaa	aaatacagac	tcgttgtctt	ggttggtccc	120
gtgggagtag	ggctgaatga	actgaaacga	aagctgctga	tcagtgcacac	ccagcactat	180
ggcgtgacag	tgccccatac	caccagagca	agaagaagcc	aggagagtga	tggtgttgaa	240
tacattttca	tttccaagca	tttgtttgag	acagatgtac	aaaataacaa	gtttattgaa	300
tatggagaat	ataaaaaaca	ctactacggc	acaagtatag	actcagttcg	gtctgtcctt	360
gctaaaaaca	aagtttggtt	gttgatgtt	cagcctcata	cagtgaagca	tttaaggaca	420
ctagaattta	agccctatgt	gatatttata	aagcctccat	caatagagcg	tttgagagaa	480
acaagaaaaa	atgcaaagat	tatttcaagc	agagatgacc	aaggtgctgc	aaaacccttc	540
acacaaggag	aatag					555

&lt;210&gt; 28

&lt;211&gt; 184

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 28

Met	Tyr	Glu	Cys	Lys	Lys	Ser	Asp	Gln	Tyr	Asp	Thr	Ala	Asp	Val	Pro
1				5				10						15	
Thr	Tyr	Glu	Glu	Val	Thr	Pro	Tyr	Arg	Arg	Gln	Thr	Asn	Glu	Lys	Tyr
			20					25					30		
Arg	Leu	Val	Val	Leu	Val	Gly	Pro	Val	Gly	Val	Gly	Leu	Asn	Glu	Leu
			35				40					45			
Lys	Arg	Lys	Leu	Leu	Ile	Ser	Asp	Thr	Gln	His	Tyr	Gly	Val	Thr	Val
			50				55				60				
Pro	His	Thr	Thr	Arg	Ala	Arg	Arg	Ser	Gln	Glu	Ser	Asp	Gly	Val	Glu
65					70				75					80	
Tyr	Ile	Phe	Ile	Ser	Lys	His	Leu	Phe	Glu	Thr	Asp	Val	Gln	Asn	Asn
				85					90					95	
Lys	Phe	Ile	Glu	Tyr	Gly	Glu	Tyr	Lys	Asn	Asn	Tyr	Tyr	Gly	Thr	Ser
			100					105					110		
Ile	Asp	Ser	Val	Arg	Ser	Val	Leu	Ala	Lys	Asn	Lys	Val	Cys	Leu	Leu
			115				120					125			
Asp	Val	Gln	Pro	His	Thr	Val	Lys	His	Leu	Arg	Thr	Leu	Glu	Phe	Lys
			130				135					140			
Pro	Tyr	Val	Ile	Phe	Ile	Lys	Pro	Pro	Ser	Ile	Glu	Arg	Leu	Arg	Glu
145					150				155					160	
Thr	Arg	Lys	Asn	Ala	Lys	Ile	Ile	Ser	Ser	Arg	Asp	Asp	Gln	Gly	Ala
				165				170						175	
Ala	Lys	Pro	Phe	Thr	Gln	Gly	Glu								
				180											

&lt;210&gt; 29

&lt;211&gt; 1563

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 29

```

atgccagctt tgtcaacggg atctgggagt gacactggtc tgtatgagct gttggctgct      60
ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat      120
atgttttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact aactactat      180
gagaagcaga gtcgggtgcc cattctccat ggtgcggcgg ccttgccga tgatctggcc      240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca      300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac      360
ccagtgttgc ctccatagcc tgaagatatt gacgatgagg aagactcagt aaaaataatc      420
cgtctggta aaaaatagaga accactggga gctaccatta agaaggatga acagaccggg      480
gcgatcattg tgccagaat catgagagga ggagctgcag atagaagtgg tcttattcat      540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaag gcctgaggaa      600
ataatacaga ttttggtcga gtctcaggga gcaattacat ttaagattat acccggcagc      660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat      720
cctaagtagg ataaggcaat tccatgtaag gaagctgggc ttctttcaa aaaggagat      780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat      840
gccaaccca gggcaggctt gatccctca aagcatttc aggaaaggag attggctttg      900
agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atctggtttt      960
agaagaagtt ttcgtcttag tagaaaagat aagaaaacaa ataaatccat gtatgaatgc     1020
aagaagagtg atcagtacga cacagctgac gtaccacat acgaagaagt gacaccgtat     1080
cggcgacaaa ctaatgaaaa atacagactc gttgtcttgg ttggtcccgt gggagtaggg     1140
ctgaatgaac tgaacgaaa gctgctgac agtgacacc agcactatgg cgtgacagtg     1200
ccccatacca ccagagcaag aagaagccag gagagtgatg gtgttgaata cattttcatt     1260
tccaagcatt tgtttgagac agatgtacaa aataacaagt ttattgaata tggagaatat     1320
aaaaacaact actacggcac aagtatagac tcagttcggg ctgtccttgc taaaaacaaa     1380
gtttgtttgt tggatgttca gcctcataca gtgaagcatt taaggacact agaatttaag     1440
ccctatgtga tatttataaa gcctccatca atagagcgtt tgagagaaac aagaaaaaat     1500
gcaaagatta tttcaagcag agatgaccaa ggtgctgcaa aacccttcac acaaggagaa     1560
tag

```

&lt;210&gt; 30

&lt;211&gt; 520

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 30

```

Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu
 1          5          10          15
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln
 20          25          30
Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His
 35          40          45
Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser
 50          55          60
Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala
 65          70          75          80
Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu
 85          90          95
Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp
100          105          110
Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu
115          120          125
Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys
130          135          140

```

```

Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly
145          150          155          160
Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser
          165          170          175
Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro
          180          185          190
Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser
          195          200          205
Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr
          210          215          220
Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
225          230          235          240
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
          245          250          255
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
          260          265          270
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
          275          280          285
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
          290          295          300
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
305          310          315          320
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
          325          330          335
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
          340          345          350
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
          355          360          365
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
          370          375          380
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
385          390          395          400
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
          405          410          415
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
          420          425          430
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
          435          440          445
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
          450          455          460
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
465          470          475          480
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
          485          490          495
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
          500          505          510
Ala Lys Pro Phe Thr Gln Gly Glu
          515          520

```

&lt;210&gt; 31

&lt;211&gt; 891

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 31

atgaaacttt tcttcagat gtttatcaaa gccctctttg actataatcc taatgaggat

60

```

aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt      120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caaccccagg      180
gcaggcttga tccctcaaaa gcatttccag gaaaggagat tggctttgag acgaccagaa      240
atattggttc agcccctgaa agtttccaac aggaaatcat ctggtttttag aagaagtttt      300
cgtcttagta gaaaagataa gaaaacaaat aaatccatgt atgaatgcaa gaagagtgat      360
cagtacgaca cagctgacgt acccacatac gaagaagtga caccgtatcg gcgacaaact      420
aatgaaaaat acagactcgt tgtcttggtt ggtcccgtgg gagtagggct gaatgaactg      480
aaacgaaagc tgctgatcag tgacacccag cactatggcg tgacagtgcc ccataccacc      540
agagcaagaa gaagccagga gagtgatggt gttgaatata ttttcatttc caagcatttg      600
tttgagacag atgtacaaaa taacaagttt attgaatatg gagaatataa aaacaactac      660
tacggcacia gtatagactc agttcggctc gtccttgcta aaaacaaagt ttgtttgttg      720
gatgttcagc ctcatagagt gaagcattta aggacactag aatttaagcc ctatgtgata      780
tttataaagc ctccatcaat agagcgtttg agagaaacaa gaaaaaatgc aaagattatt      840
tcaagcagag atgaccaagg tgctgcaaaa cccttcacac aaggagaata g              891

```

&lt;210&gt; 32

&lt;211&gt; 296

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 32

```

Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
 1              5              10              15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
      20              25              30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
      35              40              45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
      50              55              60
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
65              70              75              80
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
      85              90              95
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
      100             105             110
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
      115             120             125
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
      130             135             140
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
145             150             155             160
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
      165             170             175
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
      180             185             190
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
      195             200             205
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
      210             215             220
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
225             230             235             240
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
      245             250             255
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
      260             265             270
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala

```

275 280 285  
Ala Lys Pro Phe Thr Gln Gly Glu  
290 295

<210> 33  
<211> 585  
<212> DNA  
<213> homo sapiens

<400> 33  
atgtgctgcc caaagactgc ttgcagaggt cccgtgggag tagggctgaa tgaactgaaa 60  
cgaaagctgc tgatcagtga caccagcac tatggcgtga cagtgcccca taccaccaga 120  
gcaagaagaa gccaggagag tgatgggtgtt gaatacattt tcatttccaa gcatttggtt 180  
gagacagatg tacaaaaataa caagtttatt gaatatggag aatataaaaa caactactac 240  
ggcacaagta tagactcagt tcggtctgtc cttgctaaaa acaaagtttg tttgttggat 300  
gttcagcctc atacagtga gcatTTaagg acactagaat ttaagcccta tgtgatattt 360  
ataaagcctc catcaataga gcgtttgaga gaaacaagaa aaaatgcaaa gattatttca 420  
agcagagatg accaagggtgc tgcaaaaacc ttcacagaag aagattttca agaaatgatt 480  
aaatctgcac agataatgga aagtcaatat ggtcatcttt ttgacaaaat tataataaat 540  
gatgacctca ctgtggcatt caaaaaaaaa aaaaaaaaaa aaaaa 585

<210> 34  
<211> 195  
<212> PRT  
<213> homo sapiens

<400> 34  
Met Cys Cys Pro Lys Thr Ala Cys Arg Gly Pro Val Gly Val Gly Leu  
1 5 10 15  
Asn Glu Leu Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly  
20 25 30  
Val Thr Val Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp  
35 40 45  
Gly Val Glu Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val  
50 55 60  
Gln Asn Asn Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr  
65 70 75 80  
Gly Thr Ser Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val  
85 90 95  
Cys Leu Leu Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu  
100 105 110  
Glu Phe Lys Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg  
115 120 125  
Leu Arg Glu Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp  
130 135 140  
Gln Gly Ala Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile  
145 150 155 160  
Lys Ser Ala Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys  
165 170 175  
Ile Ile Ile Asn Asp Asp Leu Thr Val Ala Phe Lys Lys Lys Lys  
180 185 190  
Lys Lys Lys  
195

<210> 35  
<211> 672



&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 35

```

atgtatgaat gcaagaagag tgatcagtag gacacagctg acgtacccac atacgaagaa      60
gtgacaccgt atcggcgaca aactaatgaa aaatacagac tcgttgtctt gggttggtccc      120
gtgggagtag ggctgaatga actgaaacga aagctgctga tcagtgcacac ccagcactat      180
ggcgtgacag tgccccatac caccagagca agaagaagcc aggagagtga tgggtgttgaa      240
tacattttca tttccaagca tttgtttgag acagatgtac aaaataacaa gtttattgaa      300
tatggagaat ataaaaacaa ctactacggc acaagtatag actcagttcg gtctgtcctt      360
gctaaaaaca aagtttgttt gttggatgtt cagcctcata cagtgaagca ttttaaggaca      420
ctagaattta agccctatgt gatatttata aagcctccat caatagagcg tttgagagaa      480
acaagaaaaa atgcaaagat tatttcaagc agagatgacc aaggtgctgc aaaacccttc      540
acagaagaag attttcaaga aatgattaaa tctgcacaga taatggaaag tcaatatggt      600
catctttttg acaaaattat aataaatgat gacctcactg tggcattcaa aaaaaaaaaa      660
aaaaaaaaaa aa                                     672

```

&lt;210&gt; 36

&lt;211&gt; 224

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 36

```

Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
 1          5          10          15
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
      20          25          30
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
      35          40          45
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
      50          55          60
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
      65          70          75          80
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
      85          90          95
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
      100          105          110
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
      115          120          125
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
      130          135          140
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
      145          150          155          160
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
      165          170          175
Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile Lys Ser Ala
      180          185          190
Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys Ile Ile Ile
      195          200          205
Asn Asp Asp Leu Thr Val Ala Phe Lys Lys Lys Lys Lys Lys Lys Lys
      210          215          220

```

&lt;210&gt; 37

&lt;211&gt; 1680

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 37

```

atgccagctt tgtcaacggg atctgggagt gacactggtc tgtatgagct gttggctgct      60
ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat      120
atgtttggtg aaaaaagcct gcattcattg gtaaaagattc atgaaaaact acactactat      180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttgccga tgatctggcc      240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca      300
aaaccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac      360
ccagtgttgc ctcctatgcc tgaagatatt gacgatgagg aagactcagt aaaaataatc      420
cgtctggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg      480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat      540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaaag gcctgaggaa      600
ataatacaga ttttggctca gtctcagga gcaattacat ttaagattat acccggcagc      660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat      720
cctaagtagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaaggagat      780
attcttcaga ttatagcca agatgatgca acttgggtggc aagcgaaaca cgaagctgat      840
gccaaaccca gggcaggctt gatccctca aagcatttcc aggaaaggag attggctttg      900
agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atctggtttt      960
agaagaagtt ttcgtcttag tagaaaagat aagaaaacaa ataaatccat gtatgaatgc     1020
aagaagagtg atcagtacga cacagctgac gtaccacat acgaagaagt gacaccgtat     1080
cggcgacaaa ctaatgaaaa atacagactc gttgtcttgg ttggtcccgt gggagtaggg     1140
ctgaatgaac tgaaacgaaa gctgctgac agtgacaccc agcactatgg cgtgacagtg     1200
ccccatacca ccagagcaag aagaagccag gagagtgatg gtgttgaata cattttcatt     1260
tccaagcatt tgtttgagac agatgtacaa aataacaagt ttattgaata tggagaatat     1320
aaaaacaact actacggcac aagtatagac tcagttcggg ctgtccttgc taaaaacaaa     1380
gtttgtttgt tggatgttca gcctcataca gtgaagcatt taaggacact agaatttaag     1440
ccctatgtga tatttataaa gcctccatca atagagcgtt tgagagaaac aagaaaaaat     1500
gcaaagatta tttcaagcag agatgaccaa ggtgctgcaa aacccttcac agaagaagat     1560
tttcaagaaa tgattaaatc tgcacagata atggaaagtc aatatggtca tctttttgac     1620
aaaattataa taaatgatga cctcactgtg gcattcaaaa aaaaaaaaaa aaaaaaaaaa     1680

```

&lt;210&gt; 38

&lt;211&gt; 560

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 38

```

Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu
1          5          10          15
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln
20          25          30
Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His
35          40          45
Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser
50          55          60
Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala
65          70          75          80
Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu
85          90          95
Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp
100         105         110
Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu
115         120         125
Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys
130         135         140
Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly
145         150         155         160

```

Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser  
 165 170 175  
 Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro  
 180 185 190  
 Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser  
 195 200 205  
 Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr  
 210 215 220  
 Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn  
 225 230 235 240  
 Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe  
 245 250 255  
 Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp  
 260 265 270  
 Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile  
 275 280 285  
 Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu  
 290 295 300  
 Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe  
 305 310 315 320  
 Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser  
 325 330 335  
 Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro  
 340 345 350  
 Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr  
 355 360 365  
 Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu  
 370 375 380  
 Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val  
 385 390 395 400  
 Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu  
 405 410 415  
 Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn  
 420 425 430  
 Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser  
 435 440 445  
 Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu  
 450 455 460  
 Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys  
 465 470 475 480  
 Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu  
 485 490 495  
 Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala  
 500 505 510  
 Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile Lys Ser Ala  
 515 520 525  
 Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys Ile Ile Ile  
 530 535 540  
 Asn Asp Asp Leu Thr Val Ala Phe Lys Lys Lys Lys Lys Lys Lys  
 545 550 555 560

&lt;210&gt; 39

&lt;211&gt; 1008

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 39

```

atgaaacttt tcttccagat gtttatcaaa gccctctttg actataatcc taatgaggat      60
aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt      120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caaccccagg      180
gcaggcttga tccctcaaaa gcatttccag gaaaggagat tggctttgag acgaccagaa      240
atattggttc agcccctgaa agtttccaac aggaaatcat ctgggttttag aagaagtttt      300
cgtcttagta gaaaagataa gaaaacaaat aaatccatgt atgaatgcaa gaagagtgat      360
cagtacgaca cagctgacgt acccacatc gaagaagtga caccgtatcg gcgacaaact      420
aatgaaaaat acagactcgt tgtcttggtt ggtcccgtgg gagtagggct gaatgaactg      480
aaacgaaagc tgctgatcag tgacaccag cactatggcg tgacagtgcc ccataccacc      540
agagcaagaa gaagccagga gagtgatggt gttgaataca ttttcatttc caagcatttg      600
tttgagacag atgtacaaaa taacaagttt attgaatatg gagaatataa aaacaactac      660
tacggcacia gtatagactc agttcggctc gtccttgcta aaaacaaagt ttgtttgttg      720
gatgttcagc ctcatcacgt gaagcattta aggacactag aatttaagcc ctatgtgata      780
tttataaagc ctccatcaat agagcgtttg agagaaacaa gaaaaaatgc aaagattatt      840
tcaagcagag atgaccaagg tgctgcaaaa cccttcacag aagaagattt tcaagaaatg      900
attaaatctg cacagataat ggaaagtcaa tatggtcatc tttttgacaa aattataata      960
aatgatgacc tcactgtggc attcaaaaaa aaaaaaaaaa aaaaaaaa      1008

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&lt;210&gt; 40

&lt;211&gt; 336

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 40

```

Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
 1          5          10          15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
 20          25          30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
 35          40          45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
 50          55          60
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
 65          70          75          80
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
 85          90          95
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
100          105          110
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
115          120          125
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
130          135          140
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
145          150          155          160
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
165          170          175
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
180          185          190
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
195          200          205
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
210          215          220
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
225          230          235          240
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys

```

```
<210> 41
<211> 636
<212> DNA
<213> homo sapiens
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```
<210> 42
<211> 211
<212> PRT
<213> homo sapiens
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31/39

Lys Ser Ala Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys  
                                   165                                  170                                  175  
 Ile Ile Ile Asn Asp Asp Leu Thr Val Ala Phe Asn Glu Leu Lys Thr  
                                   180                                  185                                  190  
 Thr Phe Asp Lys Leu Glu Thr Glu Thr His Trp Val Pro Val Ser Trp  
                                   195                                  200                                  205  
 Leu His Ser  
                                   210

&lt;210&gt; 43

&lt;211&gt; 723

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 43

atgtatgaat	gcaagaagag	tgatcagtag	gacacagctg	acgtacccac	atacgaagaa	60
gtgacaccgt	atcgcgaca	aactaatgaa	aaatacagac	tcgttgctct	ggttggtccc	120
gtgggagtag	ggctgaatga	actgaaacga	aagctgctga	tcagtgcacac	ccagcactat	180
ggcgtgacag	tgccccatac	caccagagca	agaagaagcc	aggagagtga	tggtgttgaa	240
tacattttca	tttccaagca	tttgtttgag	acagatgtac	aaaataacaa	gtttattgaa	300
tatggagaat	ataaaaacaa	ctactacggc	acaagtatag	actcagttcg	gtctgtcctt	360
gctaaaaaca	aagtttgttt	gttggtgtt	cagcctcata	cagtgaagca	tttaaggaca	420
ctagaattta	agccctatgt	gatatttata	aagcctccat	caatagagcg	tttgagagaa	480
acaagaaaaa	atgcaaagat	tatttcaagc	agagatgacc	aaggtgctgc	aaaacccttc	540
acagaagaag	attttcaaga	aatgattaaa	tctgcacaga	taatggaaa	tcaatatggt	600
catctttttg	acaaaattat	aataaatgat	gacctactg	tggcattcaa	tgagctcaaa	660
acaacttttg	acaaaattaga	gacagagacc	cattgggtgc	cagtgcagctg	gttacattca	720
taa						723

&lt;210&gt; 44

&lt;211&gt; 240

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 44

Met	Tyr	Glu	Cys	Lys	Lys	Ser	Asp	Gln	Tyr	Asp	Thr	Ala	Asp	Val	Pro
1				5					10					15	
Thr	Tyr	Glu	Glu	Val	Thr	Pro	Tyr	Arg	Arg	Gln	Thr	Asn	Glu	Lys	Tyr
			20					25					30		
Arg	Leu	Val	Val	Leu	Val	Gly	Pro	Val	Gly	Val	Gly	Leu	Asn	Glu	Leu
		35					40					45			
Lys	Arg	Lys	Leu	Leu	Ile	Ser	Asp	Thr	Gln	His	Tyr	Gly	Val	Thr	Val
		50				55					60				
Pro	His	Thr	Thr	Arg	Ala	Arg	Arg	Ser	Gln	Glu	Ser	Asp	Gly	Val	Glu
65					70					75					80
Tyr	Ile	Phe	Ile	Ser	Lys	His	Leu	Phe	Glu	Thr	Asp	Val	Gln	Asn	Asn
			85						90					95	
Lys	Phe	Ile	Glu	Tyr	Gly	Glu	Tyr	Lys	Asn	Asn	Tyr	Tyr	Gly	Thr	Ser
			100					105					110		
Ile	Asp	Ser	Val	Arg	Ser	Val	Leu	Ala	Lys	Asn	Lys	Val	Cys	Leu	Leu
		115					120					125			
Asp	Val	Gln	Pro	His	Thr	Val	Lys	His	Leu	Arg	Thr	Leu	Glu	Phe	Lys
		130					135				140				
Pro	Tyr	Val	Ile	Phe	Ile	Lys	Pro	Pro	Ser	Ile	Glu	Arg	Leu	Arg	Glu
145					150					155					160
Thr	Arg	Lys	Asn	Ala	Lys	Ile	Ile	Ser	Ser	Arg	Asp	Asp	Gln	Gly	Ala

<400> 46  
Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu  
1 5 10 15  
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln  
20 25 30

Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His  
 35 40 45  
 Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser  
 50 55 60  
 Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala  
 65 70 75 80  
 Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu  
 85 90 95  
 Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp  
 100 105 110  
 Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu  
 115 120 125  
 Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys  
 130 135 140  
 Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly  
 145 150 155 160  
 Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser  
 165 170 175  
 Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro  
 180 185 190  
 Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser  
 195 200 205  
 Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr  
 210 215 220  
 Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn  
 225 230 235 240  
 Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe  
 245 250 255  
 Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp  
 260 265 270  
 Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile  
 275 280 285  
 Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu  
 290 295 300  
 Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe  
 305 310 315 320  
 Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser  
 325 330 335  
 Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro  
 340 345 350  
 Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr  
 355 360 365  
 Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu  
 370 375 380  
 Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val  
 385 390 395 400  
 Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu  
 405 410 415  
 Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn  
 420 425 430  
 Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser  
 435 440 445  
 Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu  
 450 455 460  
 Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys  
 465 470 475 480



```

Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
      485                      490                      495
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
      500                      505                      510
Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile Lys Ser Ala
      515                      520                      525
Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys Ile Ile Ile
      530                      535                      540
Asn Asp Asp Leu Thr Val Ala Phe Asn Glu Leu Lys Thr Thr Phe Asp
545                      550                      555                      560
Lys Leu Glu Thr Glu Thr His Trp Val Pro Val Ser Trp Leu His Ser
      565                      570                      575

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<210> 47  
 <211> 1059  
 <212> DNA  
 <213> homo sapiens

```

<400> 47
atgaaacttt tcttccagat gtttatcaaa gccctctttg actataatcc taatgaggat      60
aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt      120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caaccccagg      180
gcaggcttga tccccctaaa gcatttccag gaaaggagat tggctttgag acgaccagaa      240
atattggttc agcccctgaa agtttccaac aggaaatcat ctggttttag aagaagtttt      300
cgtcttagta gaaaagataa gaaaacaaat aaatccatgt atgaatgcaa gaagagtgtat      360
cagtacgaca cagctgacgt acccacatac gaagaagtga caccgtatcg gcgacaaact      420
aatgaaaaat acagactcgt tgtcttggtt ggtcccgtgg gagtagggct gaatgaactg      480
aaacgaaagc tgctgatcag tgacaccacg cactatggcg tgacagtgcc ccataccacc      540
agagcaagaa gaagccagga gagtgatggt gttgaatata ttttcatttc caagcatttg      600
tttgagacag atgtacaaaa taacaagttt attgaatatg gagaatataa aaacaactac      660
tacggcacaa gtatagactc agttcgggtc gtccttgcta aaaacaaagt ttgtttgttg      720
gatgttcagc ctcatacagt gaagcattta aggacactag aatttaagcc ctatgtgata      780
tttataaagc ctccatcaat agagcgtttg agagaacaa gaaaaaatgc aaagattatt      840
tcaagcagag atgaccaagg tgctgcaaaa cccttcacag aagaagattt tcaagaaatg      900
attaaatctg cacagataat ggaaagtcaa tatgtcatc tttttgacaa aattataata      960
aatgatgacc tcaactgtggc attcaatgag ctcaaaacaa cttttgacaa attagagaca     1020
gagaccattt ggggtgccagt gagctggtta cattcataa                               1059

```

<210> 48  
 <211> 352  
 <212> PRT  
 <213> homo sapiens

```

<400> 48
Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
  1                      5                      10                      15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
      20                      25                      30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
      35                      40                      45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
      50                      55                      60
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
65                      70                      75                      80
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
      85                      90                      95

```

Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser  
 100 105 110  
 Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro  
 115 120 125  
 Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr  
 130 135 140  
 Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu  
 145 150 155 160  
 Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val  
 165 170 175  
 Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu  
 180 185 190  
 Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn  
 195 200 205  
 Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser  
 210 215 220  
 Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu  
 225 230 235 240  
 Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys  
 245 250 255  
 Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu  
 260 265 270  
 Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala  
 275 280 285  
 Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile Lys Ser Ala  
 290 295 300  
 Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys Ile Ile Ile  
 305 310 315 320  
 Asn Asp Asp Leu Thr Val Ala Phe Asn Glu Leu Lys Thr Thr Phe Asp  
 325 330 335  
 Lys Leu Glu Thr Glu Thr His Trp Val Pro Val Ser Trp Leu His Ser  
 340 345 350

&lt;210&gt; 49

&lt;211&gt; 1906

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 49

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&lt;210&gt; 50

&lt;211&gt; 5426

&lt;212&gt; DNA

&lt;213&gt; homo sapiens

&lt;400&gt; 50

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